Anja Reichert

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/051086	10.03.2005	11.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07D207/48, A61K31/40, A61K31/4025, C07D403/12, C07D401/12, C07D409/12

Applicant
ALTANA PHARMA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Frelon, D Telephone No. +49 30 25901-312

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 18-20

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 18-20 with regard to industrial applicability

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item III

Claims 18 to 20 are directed to methods for treatment of the human or animal body by surgery or therapy. It relates to subject-matter considered by the ISA to be covered by the provisions of Rule 67.1(iv) PCT.

For the assessment of the present claims 18 to 20 on the question whether their subject-matter is industrially applicable, no unified criteria exist in the PCT Contracting States. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treament and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Under the terms of Rule 39.1(iv) PCT, the ISA was not required to carry out a search of such claims, but as indicated in the ISR, the search was carried out and based on the alleged effects of the compounds. Similarly, the IPEA (which is the ISA) is not required to carry out an International preliminary examination of such claims, but as for the ISR, the IPER will be based on the alleged effects of the compounds (Rule 67.1 (iv) PCT).

Re Item V

1. Cited documents

D1: WO 01/38322

D2: MILLER THOMAS A ET AL: JOURNAL OF MEDICINAL CHEMISTRY, vol. 46, no. 24, 2003, pages 5097-5116

D3: MAI, ANTONELLO ET AL: JOURNAL OF MEDICINAL CHEMISTRY, vol. 47, no. 5, 2004, pages 1098-1109

D4: MAI, ANTONELLO ET AL: JOURNAL OF MEDICINAL CHEMISTRY, vol. 46, no. 4, 2003, pages 512-524

D5: BOUCHAIN, GILIANE ET AL: JOURNAL OF MEDICINAL CHEMISTRY, vol. 46, no. 5, 2003, pages 820-830

D6: REMISZEWSKI STACY W: CURRENT OPINION IN DRUG DISCOVERY & DEVELOPPEMENT, vol. 5, 2002, pages 487-499

2. Novelty

The present subject-matter differs essentially from the prior art by the disposition of the central pyrrol ring attached to a sulfonyl group.
In D1 and D2, the two ends R6-SO_2- and -(R2)C=C(R3)-CO-NH-R7 are already disclosed in connection with HDAC inhibiting agents. They are linked to each other through an unsaturated system (delocalised electrons) in place of the pyrrol according to the invention: see examples 16, 18, 87-91, 93-120, 122, 123, 136, 159-168 and 170 of D1; oxamflatin (compound 9) and compounds of tables 7, 8 and 12 of D2.
In D3 (compounds 1a, 1b and table 1) and D4 (table 1), the central pyrrol is present but attached to a carbonyl group.

3. Inventive step

3.1 The problem underlying the present application is to provide HDAC inhibitors which are useful in the treatment of cancer, rheumatoid arthritis, Huntington's disease or inflammatory disease. All prior art compounds cited possess the activity.

3.2 The closest state of the art seen in D1 to D2 teaches that the presence of the (hetero)aromatic ring-sulfonyl-[ring including unsaturated link]-hydroxamic/2-aminobenzamide sequence is necessary for the HDAC inhibiting activity.

A structurally close skeleton is observed in compounds of D3 and D4: here a carbonyl link is in place of the sulfonyl link, but the skilled person is well aware of the usual equivalence of these groups (see for instance D1 which illustrates this known fact in its definition of the link W). Furthermore D3 an D4 teach that the unsaturated link can be a pyrrol conjugating link.

Figures 1 and 5 of D3 indicate some possible variations of the basic core which is also

shown on its binding mode in figure 6 of D4. Additionally, compound 16 of D5 confirms the relative variability of the central (hetero)aromatic ring (here a pyridine ring in place of the pyrrol according to the present application or D3 and D4 or in place of the phenyl according to D1 and D2).

D5 describes also compound 11 of figure 4 as a histone deacetylase inhibitor. This compound essentially differ by a phenyl ring in place of the pyrrol and a NH link in place of the T1 link.

Finally figure 14 of D2 illustrates the isosteric relationship which covers common elements of the central part of the molecules, *i.e.* the features which appear essential to the biological activity.

The skilled person will combine the prior art teachings and come directly to the present subject-matter expecting that they are active HDAC inhibitors. The provided tests confirm this expectation but they do not demonstrate that the particular feature which differentiates the invention vis-à-vis the state of the art (*i.e.* the sulphonyl linked to the pyrrol nitrogen atom) originates an unexpected effect. In order to substantiate the presence of an inventive step by way of comparative tests, the comparison should have been run between compounds which differ only by the said distinguishing feature.

Note the reference to the commercial utility (page 60) is not usually an argument for inventivity.

4. Miscellaneous

4.1 Since examples are, by definition, illustrative of the invention, they normally should not serve any limiting purpose. Any expression like "the scope is not limited only to those described characteristics or embodiments" or "the examples serve to illustrate the invention further without restricting it" is superfluous and should be avoided.

Any expression or sentence which may also refer to an extent of protection beyond the actual invention like "modifications (...) to the described invention (...) without departing from the spirit and scope of the invention" is also objectionable. Furthermore the reference

to an "implicite or inherent disclosure" is irrelevant.

The insertion of such sentences would suggest that the subject-matter as presently disclosed does not cover properly the claimed scope. Any expression which can be interpreted as an unjustified extension of the claimed scope should be objected. The specification should be clear and sufficient by itself. A precautionary measure on the limits of the scope is therefore superfluous and even misleading as it finally prevents a proper definition of the invention and opens the way to speculations (of skilled persons) about the very inventive subject-matter. Consequently any element against clarity has to be deleted.

4.2 References to methods of treatment or diagnostic methods as "embodiments" of the invention must be avoided as they infringe the PCT requirements. Terms and/or passages which are not essential to the definition and the understanding of the invention as claimed are superfluous and therefore do not need to appear and to be defined in the description.

Re Item VII

To meet the requirements of Rule 27(1)b) EPC, cited prior art documents should be identified in the description and the relevant background art disclosed therein should be briefly discussed.